DETAILED ACTION

Claims 1-26 and 28-59 are presented for examination.

Applicant's Amendment filed September 30, 2009 has been received and entered into the present application. Pursuant to the notice dated January 25, 2010, the amendment filed September 30, 2009 was non-compliant. Applicant's subsequent Amendment filed February 25, 2010 correcting the deficiency has also been received and entered into the present application, but was also non-compliant. Pursuant to a telephone conversation with Applicant's representative Peter Thurlow (Reg. No. 47,138) on March 31, 2010, Applicant's submission filed February 25, 2010 was also non-compliant and a corrected claim listing was requested by the Examiner. Applicant's amendment filed March 31, 2010 correcting this deficiency in the claim listing has been received and entered into the present application.

Claims 1-26 and 28-59 are pending. Claims 1-23, 28 and 40-57 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b). Claim 27 is cancelled. Claim 59 is newly added. Claims 24-26, 29-39 and 58-59 are under examination.

Examination of the instant claims has been performed insofar as the claims read on the species of (a) amitriptyline as the antidepressant (i.e., specifically, a tricyclic antidepressant as recited in instant claim 30); (b) ketamine as the NMDA receptor antagonist; (c) TRANSCUTOL P (ethoxydiglycol) as the lipophilic intradermal penetration enhancer; and (d) simethicone as the antifoaming agent.

Applicant's arguments, filed September 30, 2009, February 25, 2010 and March 31, 2010, have been fully considered. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Error Noted in the Claim Listing Filed March 31, 2010

Applicant has failed to conclude present claim 58 with a period as it was previously presented in the immediately prior version of the claims dated April 28, 2008. Since this discrepancy between the instant claim listing filed March 31, 2010 and the prior (compliant) claim listing dated April 28, 2008 does not alter the metes and bounds of the subject matter circumscribed by instant claim 58, a non-compliant notice was not sent and examination has proceeded. However, Applicant is reminded of the requirements of 37 C.F.R. 1.121(c) for proper amendments to the claims.

Objection to the Claims (New Grounds of Objection)

Claim 58 is objected to for failing to conclude with a period.

Claim 24 is objected to for reciting the term "hydrohytryptamine", which is properly spelled ---hydroxytryptamine---. In addition, Applicant's amendment to define the acronym "HT" as "hydrohytryptamine", though misspelled, has been noted. However, the claim fails to provide any indication that the acronym "HT" is intended to be equivalent to "hydrohytryptamine". Applicant may wish to consider amending the claim in the following manner to overcome this objection:

---an neurokinin 1 receptor antagonist, a 5 hydroxytryptamine [HT] ~~hydrohytryptamine~~ sub.1A receptor agonist, a 5HT.sub.1A receptor antagonist, a 5HT.sub.1A receptor partial agonist, an atypical antidepressant---.

Furthermore, Applicant has amended the claim the define the acronym as "N-methyl-D-aspartate" and has deleted the acronym "NMDA" from part (b) of instant claim 24, but fails to provide any indication that the acronym "NMDA" used later in the claims is intended to be synonymous with "N-methyl-D-aspartate". Applicant may wish to consider amending the claim in the following manner to overcome this objection:

---(b) a therapeutically effective amount of an N-methyl-D-aspartate receptor antagonist [NMDA] or a pharmaceutically acceptable salt thereof---.

Claim 33 is objected to for defining the acronym "PCP" as phencyclidine but then deleting the acronym from the claim. This is because the claim fails to provide any indication that the acronym "PCP" used later in the claims is intended to be synonymous with "phencyclidine". Applicant may wish to consider amending the claim in the following manner to overcome this objection:

---wherein the NMDA receptor antagonist is one that binds to the NMDA receptor at the glycine binding site, the glutamate binding site, the phencyclidine [PCP] binding site, the polyamine binding site, or the zinc binding site---.

Applicant is reminded that the adoption of these suggestions *supra* does not necessarily equate to the obviation of any other objection and/or rejection set forth *infra*.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30 and 35 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention, for the reasons of record set forth at p.5-6 of the previous Office Action dated March 31, 2009, of which said reasons are herein incorporated by reference.

Applicant traverses the instant rejection, stating that the claim is intended to circumscribe the use of a pharmaceutically acceptable salt of any one of the compounds recited in the claim. Applicant references para.[0047] of the published application to provide a definition of the term "pharmaceutically acceptable salt(s)".

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

The claims remain rejected because Applicant has failed to clarify, *in the claims*, whether the phrase "or a pharmaceutically acceptable salt thereof" in l.7 of each of claims 30 or 35 modifies the compound that directly precedes it or whether it is intended to circumscribe the use of a pharmaceutically acceptable salt of *any* one of the compounds recited in the claim(s). Though Applicant's statement that the claims are "intended to circumscribe the use of a pharmaceutically acceptable salt of any one of the compounds recited in the claim" (p.13, Remarks) has been noted, the actual claim language has not been modified to reflect this intention. Applicant is reminded that it is the claims that must be able to stand alone in defining the invention fully, clearly and precisely and, thus, the lack of clarification in the claims as presently written regarding which compounds can be used in the form of pharmaceutically acceptable salts fails to convey the metes and bounds of the subject matter for which Applicant is seeking protection to one of skill in the art. In addition, the disclosure at para.[0047] has been noted, but simply describes the type of salts that are encompassed by the term "pharmaceutically acceptable salt", including acidic or basic salts, and provide no further clarification that the term itself is defined as circumscribing salts of any one of the compounds recited in instant claims 30 or 35.

For these reasons *supra*, and those previously made of record at p.5-6 of the Office Action dated March 31, 2009, rejection of claims 30 and 35 is proper.

Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-26, 30, 32-37, 39 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, the recitation of the phrase "or a pharmaceutically acceptable salt thereof" in l.15-16 of instant claim 24 does not clearly, precisely or deliberately set forth whether the phrase modifies the antidepressant that directly precedes it (i.e., use of a pharmaceutically acceptable salt of an "other antidepressant") or whether it is intended to circumscribe the use of a pharmaceutically acceptable salt of *any* one or more of the antidepressants recited in the claim. In other words, the intended antecedent basis for the term "thereof" in the phrase "pharmaceutically acceptable salt thereof" is unclear because the claim as presently written fails to clearly set forth whether it is intended to circumscribe only pharmaceutically acceptable salts of "an other antidepressant" compound or whether it is intended to circumscribe pharmaceutically acceptable salts of any one or more of the antidepressant compounds listed in the claim. As a result, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection. Clarification is requested.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Present claim 59 recites that the NMDA receptor antagonist is one that binds to the NMDA receptor at the glycine binding site, the glutamate binding site, the phencyclidine binding site, the polyamine binding site, or the zinc binding site, and wherein the NMDA receptor antagonist is one that binds to the NMDA receptor at the PCP binding site.

In particular, instant claim 59 recites a broad limitation (i.e., that the NMDA antagonist is one that can bind to the NMDA receptor at any one of the glycine binding site, the glutamate binding site, the phencyclidine binding site, the polyamine binding site or the zinc binding site) followed by a narrow

limitation (i.e., that the NMDA antagonist binds at the phencyclidine binding site). The recitation of a broad limitation together with a narrow limitation that falls within the broad limitation in the same claim renders claim 59 indefinite, because the metes and bounds of the subject matter has not been clearly set forth. This is because the claim fails to clearly set forth whether the ability of the NMDA antagonist to bind at the phencyclidine binding site is merely an exemplary function or if it is a required feature of the claims. As a result, the claims fail to clearly, precisely and deliberately set forth whether the NMDA receptor antagonist can bind to the NMDA receptor at any one of the glycine binding site, the glutamate binding site, the phencyclidine binding site, the polyamine binding site or the zinc binding site or if it is required to bind at the phencyclidine binding site. As a result, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the scope of subject matter for which Applicant is presently seeking protection.

For these reasons, the claim fails to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and is, thus, properly rejected.

For the purposes of examination, Applicant is reminded that the instant claims are under examination insofar as they read upon the elected NMDA receptor antagonist, i.e., ketamine, which is defined at p.16 of the instant specification as an NMDA receptor antagonist that binds at the phencyclidine (PCP) binding site, and, thus, appears to meet either the broad or narrow limitation recited in newly added claim 59.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24-26, 29-39 and 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ford (U.S. Patent No. 6,461,600; Issued October 2002, Filed July 2001) in view of Remington's Pharmaceutical Sciences (Fifteenth Edition, 1975; p.327-339, 1452-1456), each already of record, for the reasons of record set forth at p.7-10 of the previous Office Action dated March 31, 2009, of which said reasons are herein incorporated by reference.

Newly amended claim 24 and newly added claim 59 are properly included in the instant rejection because Ford teaches a topical pain relief composition and carrier, comprising squalene NF, an emulsifier such as TWEEN 80, glycerin, cetyl alcohol NF, glyceryl monostearate (i.e., meets Applicant's limitation directed to a "surfactant" as in instant claim 24 per Applicant's definition of "surfactant" at p.19 of the instant specification, which is defined as, *inter alia*, glyceryl monostearate), lecithin organogel preserved, BHT, urea USP, EDTA, water, stearic acid (i.e., meets Applicant's limitation directed to a "lipophilic component" as in instant claim 24 per Applicant's definition of lipophilic component" at p.17 of the instant specification, which is defined as, *inter alia*, stearic acid), simethicone USP as an anti-foaming agent (instant claim 58), ethoxydiglycol (i.e., Applicant's elected species of lipophilic intradermal penetration enhancer), wherein the carrier is in combination with either or both of ketamine hydrochloride (i.e., Applicant's elected species of NMDA receptor antagonist; note also that Applicant defines ketamine at p.16 of the instant specification as an NMDA receptor antagonist that binds at the PCP site as required

by instant claims 33-34 and 59) and amitriptyline hydrochloride (i.e., Applicant's elected species of antidepressant, specifically, a tricyclic antidepressant, which is recited in instant claim 30 and provided for in instant claim 24 as an "other antidepressant"), which are each topically applied analgesic compounds (abstract). Ford further teaches that the composition comprises the above-described carrier with the two active ingredients, wherein ketamine hydrochloride is present in an amount of between 3 mg/ml and 150 mg/ml (with a preferred amount of 5 mg/ml of carrier) and amitriptyline hydrochloride in an amount of between 5 mg/ml and 20 mg/ml (with a preferred amount of 10 mg/ml of carrier) (col.2, l.7-12). Ford discloses that the preparations according to the instant invention are suitable for treating pain and pain-related conditions, including intractable pain that is non-responsive to opioids, myofascial pain, postherpetic neuralgia, neuropathic pain, etc. (col.3, l.65-col.4, l.9).

Ford fails to teach that the disclosed preparation is an oil-in-water emulsion as required by newly amended claim 24 and newly added claim 59.

Remington's Pharmaceutical Sciences is cited for its teachings that the majority of convention emulsions in pharmaceutical use have dispersed particles ranging in diameter from 0.1-100 microns (col.1, para.2, p.327). Remington's also teaches that compounds with an HLB range of from 8-18 are used as O/W emulsifying agents and those with an HLB value of from 10-18 are also effective solubilizing agents (Table VI, p.334). Further, Remington's discloses that the compound TWEEN 80 (also known as polyoxyethylene sorbitan monooleate) has an HLB value of 15.0 (Table VII, p.335) and stearic acid has an HLB value of 17.0 for O/W emulsions (Table VIII, p.336).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious that the disclosed preparation of Ford would have been, specifically, an oil-in-water (O/W) emulsion because, as evidenced by Remington's, the use of agents with HLB values between 8-18 are effective to form O/W emulsions and at least two of the emulsifying agents used in the composition of Ford have high HLB values suggestive of their activity as O/W emulsifying agents (i.e., HLB of TWEEN

80=15.0 and HLB of stearic acid=17.0). Such teachings clearly raise the reasonable expectation of success that the final product of the formulation disclosed by Ford would have been in the form of an O/W emulsion, as instantly claimed, absent factual evidence to the contrary.

Any differences between the disclosure to Ford and the instantly claims not specifically addressed *infra* are maintained as obvious for the reasons already set forth in the original rejection at p.7-10 of the Office Action dated March 31, 2010, which are not specifically repeated herein so as not to burden the record.

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that Ford in view of Remington's fails to disclose the features in amended claim 24, specifically, that the antidepressant is of those now recited in claim 24. Still further, Applicant asserts that Ford in view of Remington's does not disclose the features of newly added claim 59.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Firstly, in response to Applicant's argument that the combination of Ford in view of Remington's fails to disclose the features of claim 24, Applicant's attention is directed *supra* to the summary of the teachings of Ford taken in view of the teachings of Remington's, which teach each and every limitation of amended claim 24, including the incorporation of the antidepressant component of the type now specified in the claim. This is because Ford expressly teaches that the carrier for the disclosed topical pain relief composition is in combination with either or both of ketamine hydrochloride and amitriptyline hydrochloride, which is, notably, the species of antidepressant (specifically, a tricyclic antidepressant, which meets Applicant's limitation of instant claim 24 directed to the antidepressant being an "other antidepressant") elected by Applicant for examination on the merits. Thus, the allegation that Ford in view of Remington's fails to teach the features of claim 24, most particularly, the antidepressant feature, is

unpersuasive in view of the factual teachings of the references as summarized *supra*. Applicant's attention is directed thereto.

Secondly, in response to Applicant's argument that the combination of Ford in view of Remington's fails to disclose the features of new claim 59, Applicant's attention is once again directed *supra* to the summary of the teachings of Ford taken in view of the teachings of Remington's, which teach each and every limitation of new claim 59. Applicant's attention is again directed thereto.

Thirdly, and lastly, Applicant has failed to provide any substantive and/or specific remarks directed to what specific elements of the instantly claimed invention he believes are lacking from the teachings of Ford in view of Remington's. In the absence of such remarks, the Examiner defers to the content of the instant rejection to support the present conclusion of obviousness.

For these reasons *supra*, and those previously made of record at p.7-10 of the Office Action dated March 31, 2010, rejection of claims 24-26, 29-39 and 58-59 is proper.

Conclusion

Rejection of claims 24-26, 29-39 and 58-59 is proper.

Claims 1-23, 28 and 40-57 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Primary Examiner, Art Unit 1614

April 14, 2010